Progress Report

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A Study of Heritable Disorders of Connective Tissue

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Summary: Clinical, genetic, and pathologic studies have been performed in relatively large series of six heritable disorders of connective tissue. (Several other minor hereditary disorders of connective tissue have also been studied.) The total number of families in which at least one affected individual has been identified is as follows for each syndrome:

The Marfan syndrome - 76 kindreds
The Ehlers-Danlos syndrome - 14 kindreds
Osteogenesis imperfecta - 112 kindreds
Pseudoxanthoma elasticum - 20 kindreds
The Hurler syndrome - 28 kindreds
Fibrodysplasia ossificans progressiva - 7 kindreds

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What are reported here are our personal observations and findings since July, 1955, when my monograph Heritable Disorders of Connective Tissue, describing our experiences up to that time, went to press.

Our tissue culture program for study of these syndromes was abandoned because of technical difficulties and greater interest in other aspects and approaches. It is still planned to pursue collaborative studies with others engaged in tissue culture studies of connective tissue.

The following relevant publications have appeared or have been prepared in the last two years:

1. McKusick, V. A.: Genetic factors in diseases of the cardiovascular system. Ann. Int. Med. 49: 556, 1958.

2. McKusick, V. A.: Hereditary diseases of connective tissue. Bull. New York Acad. Med., March, 1959.

3. McKusick, V. A.: Heritable Disorders of Connective Tissue. St. Louis: C. V. Mosby Co., 1959 (2nd and revised edition).

4. McKusick, V. A.: Genetic factors in diseases of connective tissue. A survey of the current state of knowledge. Am. J. Med., Feb., 1959.

The Marfan Syndrome

1. Ventricular septal defect in unequivocal Marfan syndrome has been observed.

2. The upper segment-lower segment measurements of growing children with the Marfan syndrome have been recorded and compared with measurements in normal sibs and other normals . Thirty-eight patients with the Marfan syndrome have been measured. In seven measurements have been made over a span of years. In two, three measurements, the longest span being 10 years, have been made. All measurements were made photographically with the patient in the nude against a measured grid.

3. Experience with cardiac surgery in one case suggests that, for the present, neither total replacement of the ascending aorta by graft or prosthesis nor plication of the ascending aorta by the Bahnson technique can be expected to be successful, mainly because of the intimate involvement of the sinuses of Valsalva and the aortic cusps themselves.

Ehlers-Danlos Syndrome

1. Acrocyanosis, a feature emphasized by European writers, has now been seen in two patients.

2. Experience with the cardiovascular aspects have been increased.

   a. Two cases with major grade abnormalities (incompletely diagnosed) have been studied in detail.

   b. Two more cases of rupture of the aorta or large juxta-aortic arteries have been identified.

3. The occurrence of multiple diverticula of the gastrointestinal tract has been documented.

4. Fragility of the gut, with repeated episodes of spontaneous colonic perforation, was found in two cases.

5. Epicanthus was a striking feature of affected persons in two families.

Osteogenesis Imperfecta

1. It has been possible to diagnose osteogenesis imperfecta in both of twin fetuses while still in utero.

2. The development and evolution of hydrocephalus in one case of OI congenita has been followed to death of the infant at two years.

3. Clinical aspects of the teeth have been studied.

4. Important initial steps have been taken toward linkage analyses in this syndrome and in the Marfan syndrome.

, a. Arrangements have been made with Dr. F. H. Allen, Jr., at the Blood Typing Center in Boston to do multiple blood groupings. Haptoglobin typing by starch gel electrophoresis has been set up in our own laboratory and testing for secretor factor is under way.

b. A program for electronic (digital) computer analysis of these and other linkage data have been initiated. Dr. James H. Renwick, of the Galton Laboratory, London, here for five months Oct. 1, 1958, to March 1, 1959, has been responsible for setting up this program in my department. IBM has given us free time to the liberal extent of 15 hours per month on the IBM 704 at the Glenn L. Martin plant in Middle River. Mrs. Jane Schulze, an experienced programmer who formerly worked on this same machine, has been hired as a permanent member of our group. As a preliminary test of the method data on ABO and nail-patella linkage have been analyzed with success.

Pseudoxanthoma Elasticum

1. Plastic surgery has been used for the skin changes of the neck in one patient.

2. The Leriche syndrome--obliterative thrombosis of the bifurcation of the aorta--has been observed in one patient with PXE. Whether the association

is merely coincidence is not clear. Vascular changes in the extremities and coronary arteries are conspicuous and well recognized.

3. Further family studies support the view that inheritance is as an autosomal recessive.

Hurler Syndrome

1. Through the collaboration of Dr. Karl Meyer at Columbia it has been possible

   a. To identify increased amounts of chondroitin sulfate B and heparitin sulfate in the urine of several of our patients.

   b. To demonstrate no apparent qualitative or quantitative difference in the two genetic varieties of the disease--the autosomal recessive and the sex-linked recessive.

2. In collaboration with Dr. Richard Lindenberg, neuropathologist in the Medical Examiner's office of the City of Baltimore, it has been possible to study the gross and microscopic morbid anatomy of this disease.

   a. Hydrocephalus due apparently to meningeal involvement as part of the mucopolysaccharide abnormality.

   b. Coronary artery disease and mucopolysaccharide deposits in the intima of the aorta and pulmonary artery simulating atherosclerosis pathologically as well as clinically.

3. Studies of the Morquio syndrome, the condition most likely to be confused with the Hurler syndrome, were conducted in two families. Absence of increased urinary mucopolysaccharide (see above) permitted definitive differentiation of borderline cases and formed the basis of analysis of differentiating clinical features.

Other Observations

One case of fibrodysplasia ossificans progressiva was observed. Noteworthy features were 1) start of the disease in the gallea aponeurotica, 2) normal serum transaminase levels in active wide-spread stages of the disease (ruling out "myositis"), 3) occurrence of short femoral necks as well as the classical microdactyly.

Plans for the future are outlined in the application for continued support.